



# Serotonin and dopamine receptors in motivational and cognitive disturbances of schizophrenia

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Negative symptoms (e.g., decreased spontaneity, social withdrawal, blunt affect) and disturbances of cognitive function (e.g., several types of memory, attention, processing speed, executive function, fluency) provide a major determinant of long-term outcome in patients with schizophrenia. Specifically, motivation deficits, a type of negative symptoms, have been attracting interest as (1) a moderator of cognitive performance in schizophrenia and related disorders, and (2) a modulating factor of cognitive enhancers/remediation. These considerations suggest the need to clarify neurobiological substrates regulating motivation. Genetic studies indicate a role for the monoamine systems in motivation and key cognitive domains. For example, polymorphism of genes encoding catecholamine-O-methyltransferase, an enzyme catabolizing dopamine (DA), affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion. On the other hand, motivation to maximize rewards has been shown to be influenced by other genes encoding DA-related substrates, such as DARPP-32 and DA-D<sub>2</sub> receptors. Serotonin (5-HT) receptors may also play a significant role in cognitive and motivational disabilities in psychoses and mood disorders. For example, mutant mice over-expressing D<sub>2</sub> receptors in the striatum, an animal model of schizophrenia, exhibit both decreased willingness to work for reward and up-regulation of 5-HT<sub>2C</sub> receptors. Taken together, genetic predisposition related to 5-HT receptors may mediate the diversity of incentive motivation that is impaired in patients receiving biological and/or psychosocial treatments. Thus, research into genetic and neurobiological measures of motivation, in association with 5-HT receptors, is likely to facilitate intervention into patients seeking better social consequences.

**Keywords: serotonin, 5-HT receptors, motivation, cognition, schizophrenia, dopamine, negative symptoms, psychosis**

## INTRODUCTION

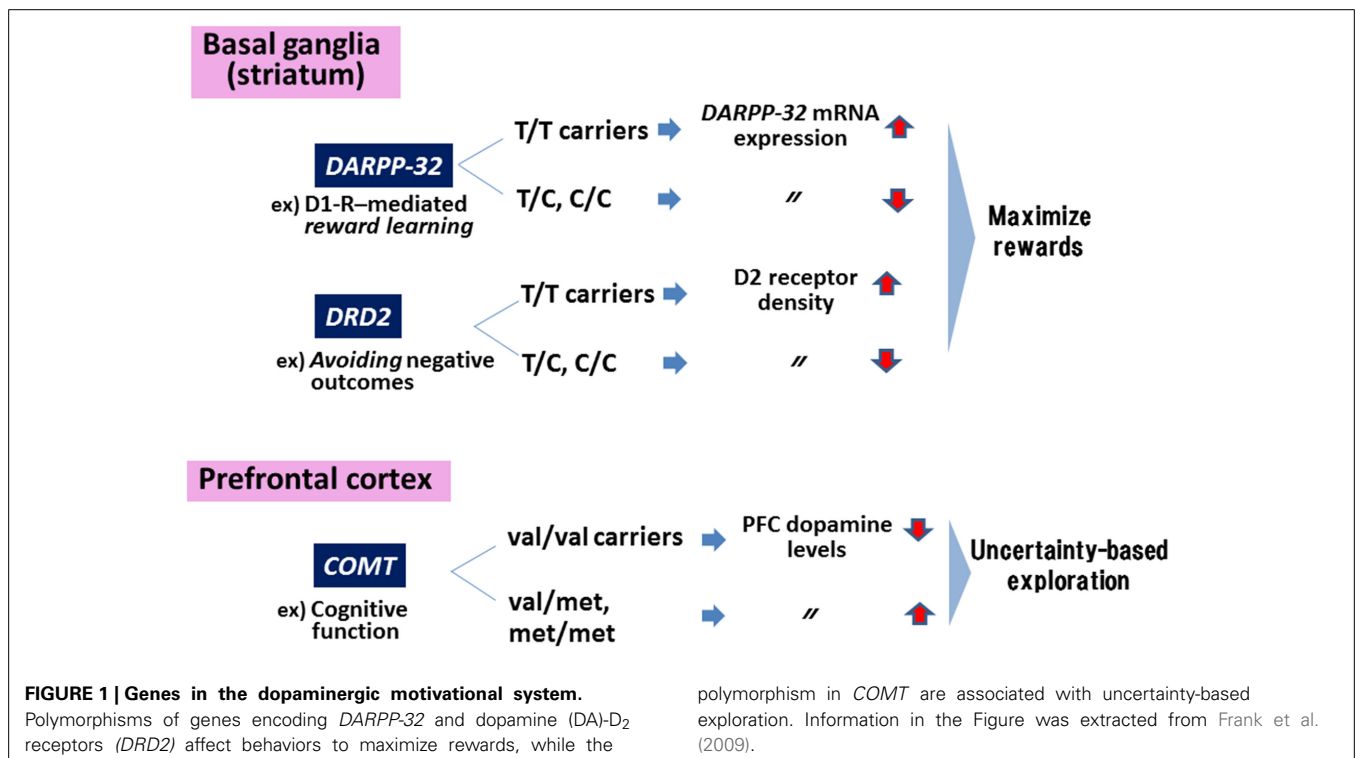
Disturbances of mental processes, including cognitive function (e.g., several types of memory, attention, processing speed, and executive function, fluency) and motivation characterize many of the psychiatric illnesses, such as schizophrenia, mood disorders, and substance abuse (Simpson et al., 2011; Choi et al., 2014; Sumiyoshi, in press). Recently, the development of biological (e.g., pharmacotherapy and brain stimulation) and psychosocial (e.g., cognitive rehabilitation) interventions is targeting social function/adaptation as an important outcome measure (Harvey et al., 2011; Leifker et al., 2011). In this context, negative symptoms (decreased spontaneity, social withdrawal, and blunt affect) and cognitive impairment provide a major determinant of long-term outcome. Specifically, motivation deficits have been attracting interest as a moderator of (1) cognitive performance in patients with schizophrenia and related disorders, and (2) beneficial influence of cognitive enhancers/remediation (Fervaha et al., 2014; Strauss et al., 2014). These considerations suggest the need to clarify neurobiological substrates regulating motivation for improving quality of life in a rational and effective manner.

We herein present a theory/hypothesis that the research into genetic and neurobiological measures of motivation, linked to serotonin (5-HT) receptors, would facilitate treatment of patients with schizophrenia or other psychiatric illnesses.

## MOTIVATIONAL DISTURBANCES IN SCHIZOPHRENIA

Schizophrenia is characterized by a range of symptoms, e.g., positive symptoms (delusions, hallucinations, thought disorders), negative symptoms, mood symptoms, and cognitive impairment. Specifically, there is a suggestion that negative symptoms can be separated into two domains; (1) a motivational dimension, consisting of avolition, anhedonia, and asociality, and (2) a diminished expressivity dimension, consisting of restricted affect and alogia (Strauss et al., 2014). There is a general consensus that motivational disturbances may overlap some (e.g., anhedonia), but not all (e.g., blunt affect, alogia) aspects of negative symptoms. The former dimension has been considered to be of greater importance in terms of functional outcome, quality of life, and recovery from the disease (Strauss et al., 2014). Whether other aspects of symptomatology of schizophrenia (e.g., mood

**Figure 1** summarizes a concept about how genes encoding these DA-related substrates contribute to cognitive and motivational behaviors.



## 5-HT RECEPTOR SUBTYPES IN MOTIVATION-RELATED BEHAVIORS

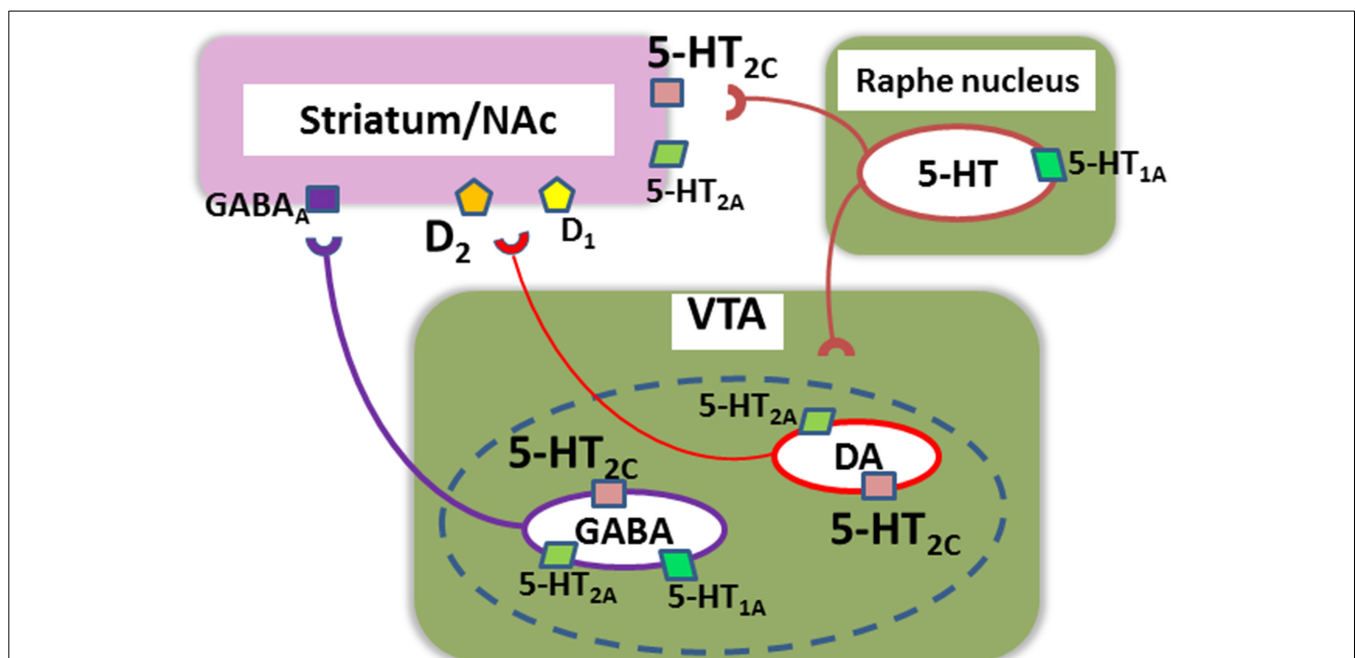
5-HT receptors, e.g., 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> subtypes, may also play a role in cognitive and motivational disabilities in psychoses and mood disorders (Meltzer and Massey, 2011; Newman-Tancredi and Albert, 2012; Ohno et al., 2012). For example, several antipsychotic and antidepressant drugs have been suggested to ameliorate negative symptoms and mood disturbances, partly through actions on 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors (Newman-Tancredi and Albert, 2012; Ohno et al., 2012; Sumiyoshi et al., 2013; Sumiyoshi, 2014). Clozapine, the prototype of atypical antipsychotic drugs, which is most effective in treating negative symptoms, may act as an inverse agonist on 5-HT<sub>2C</sub> receptors (Meltzer and Massey, 2011).

Data from recent investigations support the contribution of 5-HT receptors to motivational behaviors. For example, mutant mice over-expressing D<sub>2</sub> receptors in the striatum, exhibit both decreased willingness to work for reward and up-regulation of 5-HT<sub>2C</sub> receptors (Simpson et al., 2011). Furthermore, increased D<sub>1</sub>, D<sub>2</sub> and 5-HT<sub>2C</sub> receptors co-exist in mice mis-expressing ADAR2, an RNA-editing enzyme, and these animals elicit altered expression of reward-related mRNAs in the brain (Akubuiro et al., 2013). Collectively, these observations indicate the importance of some 5-HT receptor subtypes, e.g., 5-HT<sub>2C</sub> receptors, in the pathophysiology and treatment of motivational disturbances associated with psychoses (Figure 2).

The role for 5-HT<sub>2C</sub> receptors in psychiatric symptoms relevant to functional outcome is also supported by observations in mice whose 5-HT-synthesizing enzyme (tryptophan hydroxylase-2) was genetically engineered (Del'Guidice et al., 2014). Thus, treatment with the 5-HT<sub>2C</sub> agonist CP809,101 ameliorated impairments in cognitive flexibility and reversal learning in these mutant animals (Del'Guidice et al., 2014).

As noted above, up-regulation of 5-HT<sub>2C</sub> receptors in the striatum may be associated with a decrease in incentive motivation (Simpson et al., 2011). Further, 5-HT<sub>2C</sub> receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also have been suggested to regulate motivation by modulating transmissions to NAc (Bubar et al., 2011) (Figure 2). It should be noted that a proportion of NAc-projecting VTA neurons may release both DA and GABA (Bubar et al., 2011). Altered balance in this complicated 5-HT<sub>2C</sub> receptor-associated network is postulated to cause reward-related disorders, such as schizophrenia, depression, and addiction (Bubar et al., 2011).

Other 5-HT receptor subtypes, such as 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, may directly or indirectly influence this neural system for motivational behaviors as well. For example, 5-HT<sub>1A</sub> receptor gene polymorphism (rs6295, C-1019G) has been associated with treatment effects on negative symptoms of schizophrenia (Reynolds et al., 2006). Figure 2 illustrates a putative neural network mediating motivational behaviors in relation to 5-HT receptors, which, together with



**FIGURE 2 | A putative neural network mediating motivational behaviors in relation to serotonin (5-HT) receptors.** (1) Up-regulation of 5-HT<sub>2C</sub> receptors in the nucleus accumbens (NAc)/striatum may be associated with a decrease in incentive motivation in mutant mice over-expressing dopamine (DA)-D<sub>2</sub> receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). SB242084, a selective antagonist at these receptors, increases incentive motivation in these

model mice. (2) 5-HT<sub>2C</sub> receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also affect motivation by modulating transmissions to NAc, including actions on D<sub>1</sub> and D<sub>2</sub> receptors (Bubar et al., 2011). The dotted line indicates that a proportion of NAc-projecting VTA neurons releases both DA and GABA (Bubar et al., 2011). (3) Other 5-HT receptor subtypes, such as 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub>, may also directly or indirectly regulate this neural system of motivational behaviors.

**Figure 1** (upper part), may suggest the contribution of DA-5-HT interactions.

## CLINICAL PERSPECTIVES AND FUTURE DIRECTIONS

Based on the discussions so far, drugs acting on some 5-HT receptor subtypes, particularly, 5-HT<sub>2C</sub> receptors, are likely to improve motivational deficits in individuals with schizophrenia. For example, SB242084, a selective antagonist at 5-HT<sub>2C</sub> receptors, has been shown to increase incentive motivation in mice over-expressing D<sub>2</sub> receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). By contrast, the 5-HT<sub>2C</sub> receptor agonist CP809,101 has been demonstrated to enhance performance on some cognitive tasks in mice with decreased 5-HT synthesis (Del'Guidice et al., 2014). These preclinical observations warrant clinical studies of the effect of agents for specific 5-HT receptor subtypes, e.g., 5-HT<sub>2C</sub> receptors, on motivational and cognitive disturbances. Specifically, it is important to see if such putative pro-motivation drugs will lead to improvement of functional outcome affected by cognitive function on which such compounds might act in variable directions.

In view of a possible influence of motivation on cognitive training, it may be interesting to determine if augmentation with pro-motivation compounds, e.g., 5-HT<sub>2C</sub> agents, would provide additional merits for cognitive and functional outcome in patients with schizophrenia. Also, whether genetic variations regarding 5-HT and/or DA receptors affect motivational response to treatment with existing pharmacological or psychosocial interventions deserves further study.

In summary, genetic predisposition related to 5-HT and DA receptors may mediate the diversity of incentive motivation that is impaired in patients with schizophrenia. This concept is expected to facilitate rational treatment with biological and/or psychosocial tools to improve social consequences for people with psychiatric illnesses.

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